CASE REPORT

Autoimmune progesterone dermatitis: clinical presentation and management with progesterone desensitization for successful in vitro fertilization

Alicia Prieto-Garcia, M.D.,[a,b] *David E. Sloane, M.D.,*[a] *Antonio R. Gargiulo, M.D.,*[c] *Anna M. Feldweg, M.D.,*[a] *and Mariana Castells, M.D., Ph.D.*[a]

[a] Division of Rheumatology, Immunology and Allergy, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts; [b] Allergy Service, Hospital General Universitario Gregorio Marañón, Madrid, Spain; and [c] Division of Reproductive Endocrinology, Department of Obstetrics and Gynecology, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts

Objective: To report clinical cases of autoimmune progesterone (P) dermatitis, its relationship to IVF, and the potential for P desensitization to treat these cases to achieve viable pregnancies.
Design: Clinical description.
Setting: Institutional hospitalary practice. Allergy Division.
Patient(s): Six patients from the Allergy Clinic consulting for cyclic rashes or anaphylaxis related to the luteal phase of the menstrual cycle. Three of the conditions were related to IVF.
Intervention(s): Skin tests were performed with P. For IVF, rapid 8- and 10-step P desensitization protocols were performed, with increasing doses administered every 20 minutes via intravaginal suppositories. A rapid oral desensitization protocol was performed in one patient who required an oral contraceptive for uterine bleeding.
Main Outcome Measure(s): Progesterone skin test results. Tolerance to P desensitization. Achievement of viable pregnancies.
Result(s): Skin tests were positive in all patients and negative in 10 controls. Desensitization was successful in four patients: three patients for IVF, resulting in viable pregnancies. Another patient achieved tolerance to oral contraceptives.
Conclusion(s): Women with autoimmune P dermatitis can be desensitized successfully to P. We provide the first evidence of successful P desensitization in patients requiring IVF culminating in successful pregnancies. (Fertil Steril® 2011;95:1121.e9–e13. ©2011 by American Society for Reproductive Medicine.)

Key Words: Autoimmune progesterone dermatitis, rapid desensitization, drug allergy, anaphylaxis, progesterone, in vitro fertilization

Autoimmune P dermatitis (APD) is a rare hypersensitivity reaction to endogenous or exogenous P characterized by a periodic skin rash during the luteal phase of the menstrual cycle. Skin lesions include urticaria, angioedema, erythema multiforme, eczema, folliculitis, papulovesicular eruptions, fixed drug eruption, purpura, or vulvovaginal pruritus (1–20). Anaphylaxis is also reported (21–23). Symptoms occur 3 to 10 days before menses, with the postovulation rise in P, ending with the onset of menstruation.

The pathogenesis is unknown. Most patients have prior exogenous P exposure (24, 25). Its uptake by antigen-presenting cells and presentation to T-helper cells may result in sensitization. Positive skin tests (ST) and intramuscular challenges to P or its derivatives have provided evidence for a Th2 immune mechanism, with acute and delayed responses (17, 26–28) consistent with both type I and type IV hypersensitivity. The detection of purified IgG antibodies to P or its derivatives suggests an autoimmune basis for the syndrome in some cases (8, 17, 29). Probably, several mechanisms are involved. In patients having anaphylaxis with negative ST, P may have a direct histamine-releasing effect on mast cells (MC) (23), because human MC express P receptors (30).

Epinephrine autoinjectors should be provided to patients having anaphylaxis. Topical or systemic corticosteroids controlled cutaneous lesions in some studies (1, 13, 21). Treatment involved anovulatory agents to suppress endogenous P (1, 13, 21, 31). When pharmacologic measures were not effective, definitive treatment was obtained through hysterectomy-oophorectomy (21, 22, 32).

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Reprint requests: Mariana Castells, M.D., Ph.D., One Jimmy Fund Way, Smith Building, Room 626D, Boston, MA 02115 (E-mail: mcastells@partners.org).

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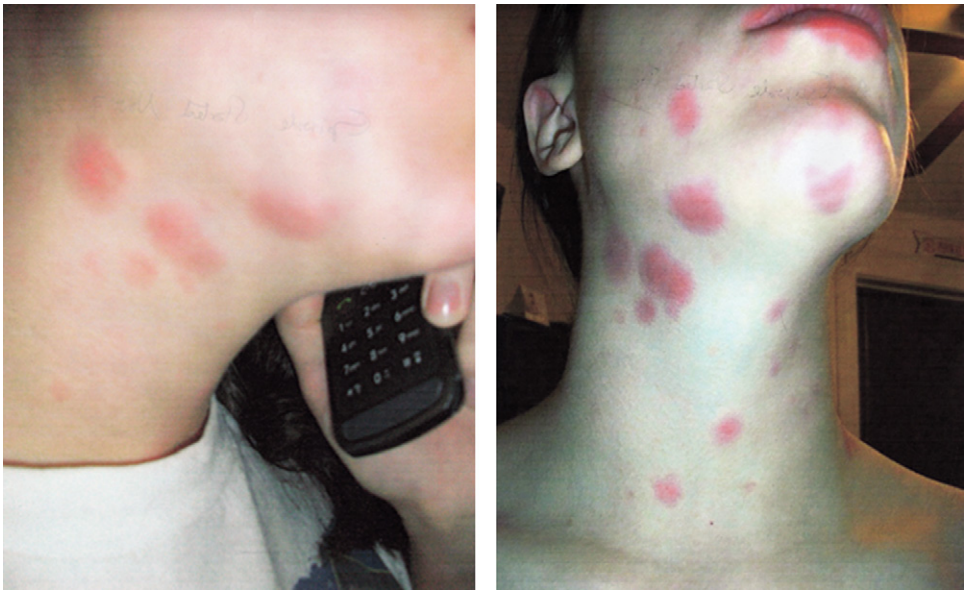
FIGURE 1

Patient 4 was seen with round, 1- to 2-cm dark, erythematous, scaly plaques on her face, neck, abdomen, chest, pelvis and lower back, which slowly faded to dark purple color but did not clear entirely before the start of her next cycle, when a new crop would appear at the same anatomic location. The previous month, she also had lip and eyelid swelling and an oral mucosa lesion. Skin lesions in two consecutive months are shown.



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Little has been reported about APD in women undergoing IVF (16), during which patients are exposed to high doses of P.

We report six cases of APD, three related to IVF and treated with desensitization, resulting in viable pregnancies. Another patient was desensitized to P, achieving tolerance to oral contraceptive pills (OCP) to treat uterine bleeding.

CASE REPORTS

Patient 1

A 39-year-old woman was seen with a perioral pruritic rash, on day 18 to 20 of each menstrual cycle, that faded and peeled after menses began. Her medical history included endometriosis, rhinitis, and asthma. At the age of 16 years, she began taking OCP. The rash developed after delivery of her first child. When she was seen initially, she was undergoing IVF. She received IM P injections and had a maculopapular rash on her face and abdomen.

Patient 2

A 43-year-old woman with primary infertility underwent three cycles of IVF. During the last cycle, she had an urticarial rash on her abdomen and periorbital swelling, lasting a few hours after P injections. Her medical history included food allergy and allergic rhinoconjunctivitis.

TABLE 1

Summary of ST results and outcome in all patients.

Patient	Positive ST	P desensitization	Outcome
1	ID 0.5 mg/mL (1/100)	Yes	Viable pregnancy (1 male)
2	ID 5 mg/mL (1/10)	Yes	Viable pregnancy (1 male)
3	ID 0.5 mg/mL (1/100)	Yes	Viable pregnancy (twins, 2 females)
4	ID 0.5 mg/mL (1/100)	Not done	—
5	ID 0.005 mg/mL (1/10,000) (benzyl alcohol 1/1,000 irritant)	Not done	—
6	ID 5 mg/mL (1/10)	Yes	OCP tolerance

Note: ST were performed with P (50 mg/mL in benzyl alcohol). Skin prick testing with undiluted drug. Intradermal testing at 1/1,000, 1/100, and 1/10 dilutions of the P solution in saline. Dilutions of benzyl alcohol were used as a negative control and histamine as a positive control. If patients had an irritant response to benzyl alcohol, ST were performed at a 10-fold lower concentration. Reading was made 15 minutes after placement. Patients were told to report any delayed ST reaction. ID = intradermal.

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Patient 3

A 36-year-old woman with primary infertility presented with anaphylaxis after P injections. She underwent three cycles of IVF in the past. She was undergoing IVF again and started daily P injections, having repeated bouts of diffuse urticaria and lip, periorbital, and hand angioedema. Subsequently, she had shortness of breath, chest tightness, lightheadness, nausea, abdominal colic, diarrhea, diaphoresis, and presyncope requiring an emergency department visit.

Patient 4

A 21-year-old woman was seen with 3 months of rash, resembling fixed drug eruption, appearing cyclically the day her menses began (Fig. 1). She denied taking nonsteroidal anti-inflammatory drugs or any other medication for dysmenorrhea. She improved with oral prednisone. The first time she noticed the rash she had started an unknown OCP for the first time, which she promptly discontinued.

Patient 5

A 39-year-old woman was seen with an extensive pruritic rash covering her entire head, breasts, and groin, which flared monthly, 10 days before her menses, clearing after her period. She had had allergic rhinitis, asthma, and mild eczema since childhood. She started having flares of her eczema with her first pregnancy, and the condition became worse with her second and third pregnancies. She was given OCP for a time, and the dermatitis was more extensive and persistent. Oral corticosteroids helped, but the rash rebounded severely when tapered. Her IgE level was 2,000 IU/mL. She was given omalizumab 5 months before presentation with some improvement in the rash, although it persisted.

Patient 6

A 33-year-old woman with dysfunctional uterine bleeding had received treatment over the past 2 years with OCP and intermittent P injections. Over this period, urticaria and angioedema developed. Her medical history included allergic rhinitis and penicillin allergy. Three months before presentation, she took 0.15 mg desogestrel–20 μg ethinyl E_2 (EE), and hives, vulvar swelling and redness, and some difficulty breathing developed. After a depot medroxyprogesterone acetate injection (150 mg) to stop heavy vaginal bleeding she had shortness of breath, cough, and chest tightness, as well as a flare of her urticaria.

MATERIALS AND METHODS

Skin tests were performed with P (Table 1). Ten healthy women underwent skin testing as negative controls. A skin punch biopsy sample was taken in patient 4.

TABLE 2

Progesterone desensitization protocols.

Protocol step	Vaginal suppositories dose (mg)	No. of suppositories	Oral capsules dose (μg)	No. of capsules	Total dose	Time interval (min)
Eight-step P desensitization protocol for patients 1 and 2						
1	0.05	1			0.05	20
2	0.05	2			0.1	20
3	0.5	1			0.5	20
4	0.5	2			1	20
5	5	1			5	20
6	5	2			10	20
7	50	1			50	20
8	50	2			100	20
Ten-step P desensitization protocol followed in patient 3[a]						
1	0.1	1			0.1	20
2	0.1	2			0.2	20
3	0.1	5			0.5	20
4	1	1			1	20
5	1	2			2	20
6	1	5			5	20
7	10	1			10	20
8	10	2			20	20
9	10	5			50	20
10	10	2			20	20
Seven-step oral P desensitization protocol followed in patient 6[b]						
1			1	1	1	30
2			1	2	2	30
3			1	5	5	30
4			10	1	10	30
5			10	2	20	30
6			10	5	50	30
7			100	1	100	30

[a] Each dose was delivered as intravaginal suppositories prepared at the hospital pharmacy with use of glycerin as vehicle. The initial dose was fivefold to 100-fold lower than the dose eliciting a positive ST, and doses increased by twofold to fivefold to achieve 100 mg. The following day the patient continued with P 100 mg three times daily.

[b] With use of capsules made at a compounding pharmacy.

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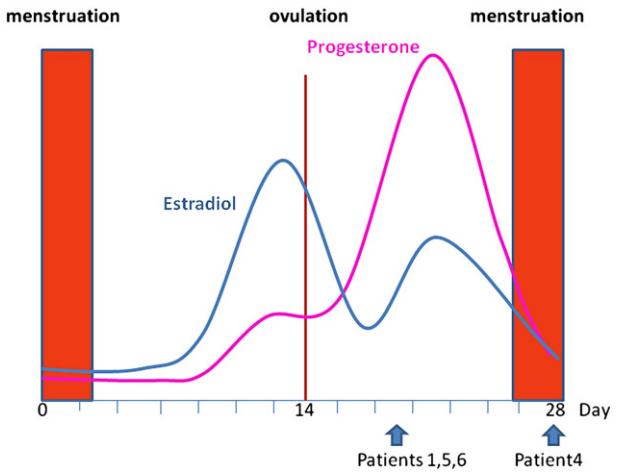
FIGURE 2

Estradiol and progesterone in the menstrual cycle. *Arrows* show the cycle day when symptoms start in each patient.



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For patients 1, 2, and 3 undergoing IVF, a P desensitization protocol was designed with use of intravaginal suppositories (Table 2). The initial dose was increased to achieve 100 mg, which is the initial target dose for inducing ovulation and implantation. A third oral protocol was administered in patient 6 (Table 2). The starting dose was 1 μg and gradually increased to 100 μg, which was the amount contained in the OCP the patient hoped to take.

RESULTS

Skin test results were positive in all six patients (Table 1) and negative in all controls.

Patient 1

Patient 1 received premedication with prednisone 40 mg/d, starting 3 days before treatment and tapering after egg transfer. She tolerated desensitization, and dermatitis did not develop. She became pregnant after two IVF treatments preceded by the P desensitization protocol. She had no rash during pregnancy. After delivery she again had the same perioral rash.

Patient 2

Prednisone was added (40 mg/d) starting 3 days before treatment and tapering after egg transfer. After the fourth cycle of desensitization and IVF, with two previous miscarriages, she became pregnant and delivered a healthy baby. She had no rash, either during pregnancy or after delivery.

Patient 3

Patient 3 underwent P desensitization as part of a new IVF cycle. Premedication with montelukast 10 mg one hour before starting the suppositories was taken, as well as 10 mg at night the following 2 days. The patient became pregnant and delivered healthy twins.

Patient 4

Skin biopsy results showed a mild interface dermatitis associated with a predominantly lymphoid infiltrate and scattered melanocytes. A detached scale was seen, but no blister was identified. She was given 0.4 mg norethindrone–35 μg EE to suppress ovulation and had no further symptoms.

Patient 5

Patient 5 was given 1 mg ethynodiol diacetate and 35 μg EE daily with a remarkable improvement.

Patient 6

Patient 6 underwent oral P desensitization protocol without any symptoms. The following day she continued with 0.1 mg levonorgestrel and 0.02 mg EE pills daily with good tolerance.

DISCUSSION

Autoimmune P dermatitis is a rare syndrome difficult to recognize because of its diverse clinical presentation. Women can suffer for many years before a diagnosis is made. When P cannot be used for IVF, it can lead to infertility. We report here the first use of P desensitization to treat APD and its combination with IVF to achieve viable pregnancies.

Especially remarkable is patient 4's presentation resembling fixed drug eruption. Skin biopsy did not show specific findings, but it was performed after corticosteroid treatment. Skin lesions appeared the first day of menstruation when P and estrogen levels are low (Fig. 2). The patient's T cells may have been demonstrating a delayed response to higher P levels a few days earlier.

When treating patients to suppress ovulation, OCP with the lowest doses of P-like hormones should be tried initially, as in patients 4 and 5 (common OCP may contain more than a 10-fold higher dose). If symptoms persist, the second step should be desensitization. But in patients with previous reaction to low-dose P OCP, desensitization likely will be necessary, as in patient 6.

In vitro fertilization treatments are being used with greater frequency, and probably APD will be observed more often. The massive exposure to supraphysiologic doses of P used for IVF may increase the likelihood of sensitization. Three of our patients had symptoms related to IVF. Patient 1 had an exacerbation of her previous APD during IVF. Patients 2 and 3 had symptoms for the first time after exogenous P administered for IVF. These latter patients did not have cyclic manifestations related to menses, which may be representative of hypersensitivity to exogenous but not endogenous P. Higher than physiologic levels or the presence of chemically slightly different P may be necessary to trigger clinical manifestations of MC activation in these cases.

Because patients require IVF and there is no alternative to P, desensitization is needed to achieve viable pregnancies. Other conditions requiring P treatment, such as uterine bleeding, may benefit from desensitization, as well.

We developed a rapid P desensitization protocol using an algorithm previously described for desensitization to other drugs (33–35). The protocols presented here were successful. None of the patients had breakthrough symptoms either during the procedure or in the following months. The addition of premedication may have increased the safety of the procedure. Maculopapular rashes were premedicated with steroids, and patient 3, who had hives and bronchospasm, received montelukast for leukotriene blockade. Finally, for the first time we provide evidence of P desensitization applied to IVF, resulting in successful pregnancies. Desensitization expands the treatment options for women with APD beyond simply suppressing ovulation and represents the only treatment option currently available that preserves the patient's fertility.

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